News from the San Antonio Breast Cancer Symposium 2013

Fink, Daniel

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Expert Discussion

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News from the San Antonio Breast Cancer Symposium 2013

Chair: Daniel Fink[a]

Participants: Stefan Aebi[b] Michael Gnant[c] Nadia Harbeck[d] Cornelia Leo[a]

[a]Klinik für Gynäkologie, UniversitätsSpital Zürich; [b]Medizinische Onkologie, Luzerner Kantonsspital, Switzerland; [c]Breast Health Center Vienna, Comprehensive Cancer Center Vienna, Medical University of Vienna, Austria; [d]Brustzentrum, Universitätsfrauenklinik, Klinikum Großhadern, Munich, Germany

Question 1: Which Patients Should Be Offered Chemoprevention?

Leo: Dr. Cuzick presented results from the phase III IBIS-II trial that evaluated whether anastrozole prevents the development of breast cancer in women at increased risk. Although anastrozole was demonstrated to significantly lower the incidence of all breast cancers and seemed to be well tolerated, the side effects still cannot be neglected. Especially musculoskeletal events and a slight increase in fracture rate are important considerations when recommending such a chemopreventive therapy in otherwise healthy women. Certainly, anastrozole – in addition to tamoxifen and exemestane – might be an option but should still be individually discussed with the woman at risk.

Gnant: Chemoprevention is always an individualized balancing for risks and benefits. Based on the IBIS-II results, I am discussing preventive anastrozole with high-risk women based on family history, in-situ lesions, and breast density.

Harbeck: Women fulfilling the IBIS-II inclusion criteria need to be informed about the possibility of chemoprevention with an aromatase inhibitor (AI). Yet, the individual decision will certainly need to balance risk for breast cancer vs. side effects and quality of life.

Question 2: How Do You Prescribe Adjuvant Bisphosphonates? (Which Patients? Which Substance? Which Dosage?)

Aebi: Given the current state of reimbursement, the adjuvant use of bisphosphonates is often not feasible. For postmenopausal patients (iatrogenic and natural menopause) I try to find osteoporosis to justify the use of zoledronic acid, and I try to get confirmation of insurance coverage for the use of 4 mg of zoledronic acid every 6 months for postmenopausal patients. Only few patients are willing to pay out of their own pocket, and in such patients, too, zoledronic acid is the drug of choice. Generic zoledronic acid is available in Europe; thus the pharmaceutical industry will likely have a low incentive to register the adjuvant use. Mechanisms that are independent of pharmaceutical companies are urgently needed to update the label of old drugs.

Gnant: Adjuvant bisphosphonates are effective in reducing bone metastases (and probably non-bone metastases to some extent) in patients with 'low-estrogen' environments. Given the lack of licensed drugs in this indication, I am discussing preventive use of zoledronic acid with premenopausal patients on ovarian function suppression and tamoxifen (based on ABCSG-12), and zoledronic acid or clodronate with clearly postmenopausal patients.

Leo: Robert Coleman introduced a meta-analysis that involved 36 trials of adjuvant bisphosphonates in breast cancer with 17,791 pre- and postmenopausal women. This analysis demonstrated a significant survival benefit for postmenopausal women who received bisphosphonates in an adjuvant setting. The type and dosage of the used bisphosphonate did not matter. This meta-analysis clearly sheds light onto the controversial discussion whether or not bisphosphonates should have a role as a standard adjuvant treatment. And with an absolute breast cancer mortality risk reduction of 3.1% this treatment can compare well to other adjuvant substances introduced over the past years. Still, the data have to be handled with caution since a huge part of the analysis is based on the AZURE patients who define the hypothesis-generating population. Since bisphosphonates are already well used in preventing bone loss associated with aromatase inhibitor use in postmenopausal women they might already prevent recur-

KARGER

Fax +49 761 4 52 07 14
Information@Karger.com
www.karger.com

1661-3791/14/0091-0066$39.50/0

Accessible online at:
www.karger.com/brc

Prof. Dr. med. Daniel Fink
Klinik für Gynäkologie
UniversitätsSpital Zürich
Frauenklinikstrasse 10, 8091 Zürich, Switzerland
daniel.fink@usz.ch

rences in that patient population. We will have to see how guideline panels assess these new data and whether they will be implemented in state-of-the-art recommendations.

Harbeck: The EBCTCG meta-analysis showed that adjuvant bisphosphonates are effective primarily in postmenopausal patients. The effect on reduction of bone metastasis and mortality was independent of hormone receptor status. It also did not differ according to type and regimen of bisphosphonates. We now offer adjuvant bisphosphonates to all postmenopausal patients and to premenopausal patients who are treated by GnRH + tamoxifen according to the ABCSG-12 results. Our preferred regimen is zoledronic acid every 6 months for 3 years.

Question 3: How Do You View Local Surgery in Case of Metastasized Disease?

Aebi: The question is still unresolved, but the 2 trials reported from India (Badwe) and Turkey (Soran) do not support local surgery for stage IV disease. The statistical analysis of both trials does not allow conclusions with regard to special populations such as patients with oligometastatic disease in whom the primary and all detectable metastatic disease could be removed by surgery. Thus, surgery of the primary for patients with stage IV disease is indicated for local palliation but should be considered experimental for all other indications.

Gnant: The idea of eliminating stem cells from the generalized disease is fascinating – however the reported trials from Tata Memorial in Mumbay and Turkey, respectively, have been negative. I am not convinced that the methodology of these trials can be viewed as sufficient to settle the issue. Further trials are ongoing and should be supported.

Harbeck: Systemic therapy is the standard in primary metastatic disease. In patients with good response, I still consider resection of the primary tumor as an option if R0 resection can be achieved. We do not have evidence that this will increase survival but individual patients may opt for it for psychological or other reasons. I do not think that the 2 trials presented at SABCS represent our therapeutic reality – we need more data to definitely rule out this option. Nevertheless, the investigators need to be congratulated for completing recruitment.

Leo: At the SABCS 2013, 2 prospective trials regarding this topic were discussed (Badwe et al., Soran et al.). Both studies did not show a survival benefit for patients that were metastasized at first presentation and who received locoregional treatment either before or after systemic therapy. These 2 important trials suggest that locoregional treatment should not be offered to stage IV patients in routine clinical practice but should be reserved for palliation for fungating or bleeding primary breast tumors.

Question 4: Should We Forego Radiation after Breast Conserving Surgery in Elderly Patients? Is There a New Standard?

Leo: Ian Kunkler presented data from the PRIME-2 randomized trial that included 1,326 patients aged 65 or older with hormone receptor-positive low-risk breast cancer. In addition to endocrine treatment, the patients either received adjuvant radiotherapy (RT) or not. Although the investigators observed a difference in 5-year ipsilateral breast tumor recurrence that favored RT, the absolute difference was small and overall survival did not differ between the groups. Interestingly, patients whose tumors had high estrogen receptor (ER) expression had a lower local recurrence rate than those with low ER expressing tumors when omitting RT. Especially for tumors with high ER expression, omission of RT in older patients represents an option that can be individually discussed with the patients. However, it is not a new standard, since the benefit of RT is still clearly shown.

Aebi: The PRIME-2 trial (reported by Kunkler) is in line with prior North American trials [Hughes RT et al. J Clin Oncol 2013;31:2382–2387 and Fyles et al. N Engl J Med 2004;351:963–970]. As such the superior local control by RT without any survival advantage is no surprise. This does not represent a new standard, as it merely confirms prior results; whether or not omission of whole breast irradiation is acceptable depends on the weight given to local control by both patients and their physicians.

Gnant: No. We have demonstrated in ABCSG-8a already several years ago that careful patient selection will result in a low locoregional relapse rate when RT is omitted after breast conservation – about 5%. However, as we have demonstrated in a randomized fashion, with RT these patients look at a 0.5% risk – significantly lower. I still believe that leaving out RT should be reserved for rare situations of very frail patients or in the situation of severe comorbidity or transportation issues.

Harbeck: So far, there is no prospective data that radiation can be safely omitted. Yet, older patients with tumor characteristics like the PRIME trial inclusion criteria need be informed that the benefit may be reduction of local failure rate but not improving survival. There are also concepts of 'less burdening' RT such as hypofractionation or IORT alone which may present alternatives to full breast irradiation after breast conserving surgery in low-risk situations.

Question 5: Beyond Estrogen Receptor, HER2, and Oncotype Dx – Do We Have New and More Precise Techniques to Identify Patients Who Will Profit from Certain Therapies?

Aebi: Further to properties of the cancers, characteristics of the patients tend to be neglected. They should be just as much in the center of attention as cancer biology: concomitant diseases and pharmacogenetic information might also influence the choice of therapy. Despite substantial advances in the biological understanding of breast cancers, no readily applicable predictors have emerged that would facilitate the choice of therapies, be it in the adjuvant or in the advanced setting.

Gnant: Techniques to identify patients who will profit from certain therapies? Definitely. Tumor proliferation (measured e.g. by Ki67) is an important tool in my daily practice, based on high-quality conventional pathology. Also, Nanostring's Prosigna® and Sividon's Endopredict® habe demonstrated excellent data, particularly for the issue of long-term risk (and thus may be useful for decision-making about extended adjuvant therapy).

Harbeck: Yes, definitely – we do have to get used to asking for more information about certain tumor types, in particular luminal ones before deciding about adjuvant chemotherapy for example. We presented the run-in phase of the WSG-ADAPT trial at SABCS and were able to show feasibility of a short-term (3-week) induction endocrine therapy before surgery in luminal tumors. Initial Oncotype DX as well as 3-week Ki-67 are then decisive for the chemotherapy decision. We expect to be able to spare about 50–60% of adjuvant chemotherapy in patients with 0–3 involved lymph nodes, in particular since in the intermediate-risk population, about 70% had a Ki-67 decrease < 10% after the 3-week endocrine therapy, indicating sufficient response to endocrine therapy alone.

Question 6: In Your Personal View, What Was the Most Relevant Finding at SABCS 2013?

Aebi: The presentation of the first results of the I-SPY 2 trial (Rugo) opens the field for a new generation of trial designs allowing a more rapid identification of drugs with potentially useful clinical activity. The statistical design is such that drugs selected by this procedure have a high probability of success in a randomized phase III trial; this may make the evaluation of the benefits of the numerous drugs in development more feasible than with traditional trial mechanisms.

Gnant: I probably have to admit to a personal bias: the final definition of the overall adjuvant bisphosphonate effect in postmenopausal women should finally settle these discussions. Based on the meta-analysis of 22,000 patients, this is a major finding.

Harbeck: I personally think that the meta-analysis on adjuvant bisphosphonates will have the greatest clinical impact since it will be decisive for clinical practice as outlined before.

Participants

Prof. Dr. med. Stefan Aebi
Medizinische Onkologie
Luzerner Kantonsspital
6000 Luzern 16, Switzerland
stefan.aebi@onkologie.ch

Prof. Dr. med. Michael Gnant, M.D., FACS
Department of Surgery
Breast Health Center Vienna
Comprehensive Cancer Center Vienna
Medical University of Vienna
1090 Wien, Währinger Gürtel 18–20, Austria
michael.gnant@meduniwien.ac.at

Prof. Dr. med. Nadia Harbeck
Brustzentrum, Universitätsfrauenklinik
Klinikum Großhadern
Marchioninistr. 15, 81337 München, Germany
Nadia.Harbeck@med.uni-muenchen.de

PD Dr. Cornelia Leo
Brustzentrum / Klinik für Gynäkologie
UniversitätsSpital Zürich
Frauenklinikstrasse 10, 8091 Zürich, Switzerland
cornelia.leo@usz.ch